PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JOH/ht		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NO00/00200	08/06/2000	08/06/1999
International Patent Classification (IPC) or national classification and IPC G01N33/53		
Applicant UNIFOB, STIFTELSEN UNIVERSITETSFORSKNING BERGEN		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/12/2000	25.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wieser, M Telephone No. +49 89 2399 8434

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NO00/00200

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-22 as originally filed

Claims, No.:

1-8 as originally filed

Drawings, sheets:

1/11-11/11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 5,8.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 5,8 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 1-4,6,7

	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-4,6,7
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-4,6,7
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Section III

SEQ ID NO 1 discloses a peptide fragment of RyR1 having 374 amino acid residues (Glu799-Asp1172). SEQ ID NO 2 discloses a peptide fragment of RyR1 having 348 amino acid residues (Arg2592-Thr2939), as can be seen from US-A-5 538 649, figure 2.

On page 9, lines 11-15 of the description, it is stated that the internal designation pc2 is identical to SEQ ID NO 1, and pc25 to SEQ ID NO 2. However, the length of the peptides indicated in this passage differs from what is shown in the sequence listings.

Consequently, claims 5 and 8, referring to a kit and a method using pc2 and/or pc25 fusion proteins, are not clear (Article 6 PCT). Since the identity of the peptides pc2 and pc25 is unclear, no meaningful opinion on novelty, inventive step and industrial applicability of these claims can be given.

Section V

The present invention seems to be based on the fact, that peptides defined by SEQ ID NO 1 and NO 2 have been identified as containing the main immunogenic region (MIR) of the ryanodine receptor (RyR). The peptides when fused to a general sequence are used in a method for detecting anti-RyR antibodies in patient samples, which are indicative of myasthenia gravis (MG). Claims 1-4, 6 and 7 refer to such method, to the use of said fusion proteins and to kits and compositions containing them.

The closest prior art results from "Autoimmunity", vol.17, 1994, pages 327-331, and from "Ann.Neurol.", vol.32, 1995, pages 589-91, disclosing methods for detecting anti-RyR antibodies, using either crude sarcoplasmatic reticulum (SR) or the whole ryanodine receptor per se as antigen, which is a large molecule of 565 kD. The present invention provides smaller molecules which can be used in ELISA tests and which moreover effect an increased sensitivity of the detection method (see page 10, table 1).

Peptides having the amino acid sequences shown in SEQ ID NO 1 and NO 2 are not disclosed in the documents cited in the International Search Report. Fusion proteins comprising said peptides are therefore novel according to Article 33(2) PCT. The same applies to claims, like present claims 1-4, 6 and 7, referring to methods and kits using, respectively containing them.

Since the known prior art documents do not contain any suggestion that would prompt a skilled person to arrive at these peptides, defining the MIR of RyR, in an obvious way, the claims are also considered to be based on a inventive concept (Article 33(3) PCT).

Section VIII

Claims 1-4, 6 and 7 are not supported by the description (Article 6 PCT). The entire application, see especially the experiments on pages 9-14, does not disclose a fusion protein comprising either SEQ ID NO 1 or NO 2. The only proteins described and used are pc2-RyR and pc25-RyR fusion proteins. For reasons explained in item III above, these designations are unclear.

Additional unclarity is introduced by a statement on page 8, lines 9-10 of the description, where it is stated that pc2-RyR fusion protein is known from a publication designated "Mygland, 1992". The only document from this author, from 1992, which is known to the Examining authority, i.e. "Ann.Neurol.", vol.32, 1995, pages 589-91, does not disclose such a fusion protein.

Claims 3,6 and 7 refer to "fusion proteins having the following sequences: SEQ ID NO 1 or SEQ ID NO 2." The Applicant is informed that this formulation is read as meaning that SEQ ID NO 1 defines a fusion protein (the same applies to SEQ ID NO 2). If the Applicant wants to express that the claimed fusion proteins contain as one part thereof a peptide having SEQ ID NO 1 or NO 2, than a formulation like for instance "fusion proteins containing either SEQ ID NO 1 or NO 2" would be clear.

Step (a) of claim 1 refers to "obtaining a serum sample from a patient". This step is considered as being a surgical method practised on the human body, which is

not considered as being industrially applicable in several legislations (for instance the EPO). In order to overcome an objection in this respect, claim 1 could be amended by deleting step (a) and reformulating step (b) to read: "contacting a serum sample obtained from a patient....".